

REMARKS

Claims 1-39 are pending. Claims 27-38 are withdrawn. New claim 40 is added herein. Therefore, claims 1-26, 39, and 40 are under consideration. Claims 1 and 25 are amended herein to recite "wherein the methanol induction is at a temperature 16.5°C and below." Claim 10 is amended herein to recite "wherein the mutation prevents ADP ribosylation of EF-2." Claims 10 and 39 are amended to correct a grammatical error. Claims 10 and 39 have been further amended to recite "a mutation in the amino acid sequence of the diphthamide region of EF-2." Claim 16 has been amended herein to remove reference to 17.5°C and 17°C which were necessitated by the amendment to Claim 1. Support for the amendment to Claims 1 and 25 can be found throughout the specification and at least on page 13, lines 13-16, Figure 15B, and in original claims 1, 16, and 25 where induction temperatures are discussed. Support for the amendment to claim 10 can be found at least on page 18, lines 21-24 of the specification. Claims 10 and 39 have been amended to correct a grammatical error as suggested by the Examiner. Support for the amendment to Claims 10 and 39 can be found throughout the specification and at least in figure 3. Support for new claim 40 can be found at least on page 18, lines 21-24 of the specification as filed, where the Glycine to Arginine substitution at amino acid residue 701 is discussed. The specification has been amended to remove reference to Figure 1a and 1b although no formal objection has been raised. Applicants believe that the above amendments do not constitute new matter nor raise new issues as all of the amendments have previously been considered by the Examiner.

Objections to the Claims

Claims 10 and 39 are objected to for allegedly containing grammatical errors. Claims 10 and 39 have been amended to recite the "amino acid sequence of EF-2." Applicants believe that the claims are now grammatically correct and respectfully request the withdrawal of the objection.

35 U.S.C. § 112, FIRST PARAGRAPH

Claims 10 and 39 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. In particular, the Examiner has rejected claims

10 and 39 as allegedly failing to provide the skilled artisan with “a representative number of species sufficient to show applicants were in possession of [the] claimed genus.” Applicants respectfully traverse this rejection.

Applicants note that claim 10 has been amended to recite “wherein the mutation prevents ADP ribosylation of EF-2,” similarly to claim 39. Also, Applicants have amended both Claims 10 and 39 to recite “a mutation in the amino acid sequence of the diphthamide region of EF-2.” Applicants respectfully point out that the standard for determining whether enough species are disclosed to provide written description for a genus is:

sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics,...or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997).

Additionally, the courts have further determined that “a ‘representative number of species’ means that the species which are adequately described are representative of the entire genus.” See *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 966, 63 USPQ2d 1609, 1615 (Fed. Cir. 2002). This means that the described species must account for the variability within the genus. Here, the only effect is the prevention of ribosylation and the only variability is the residues within the ribosylation site that are modified. Applicants provide description of at least two species within the claimed genus. Specifically, Applicants describe mutants with substitutions at residue 699 and 701 at least in Figure 1 and on page 18, line 9 through page 19, line 15. Moreover, both of these mutants have the desired effect of preventing ADP ribosylation. Therefore, Applicants respectfully assert that these two species constitute a representative number of species. Even if one of the mutations Applicants describe is not deemed a mutant, Applicants have still described at least the mutation at residue 701 and this single mutant is a sufficient number of species. In fact, the courts have specifically held that “there may be situations where one species adequately supports a genus.” See *In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326-327 (CCPA 1981).

Applicants respectfully contend that it is a long established tenant of patent law that what

constitutes a “representative number” is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a “representative number” depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed (MPEP 2163(II)(A)(3)(a)). Here, Applicants claim mutants that affect the ADP ribosylation of EF-2. The Examiner concedes that “[i]t is clear from the specification that this mutation must allow production of EF-2 but must affect the ability of EF-2 to be ADP ribosylated.” Applicants have described the ribosylation site as being a 22 amino acid sequence located between residues 690 and 842. Thus, not only would the skilled artisan would clearly understand that Applicants were in possession of mutants that affect ADP ribosylation site, also the skilled artisan would understand that the ADP ribosylation site is a conserved 22 amino acid sequence as indicated by at least Figures 1 and 3. Thus, the only possible mutants in the genus are those affecting this 22 amino acid sequence. The Examiner has equated all possible substitutions and deletions at a particular residue as a single mutation (see page 5 of the present office action where the Examiner states “modification of the His residue....is a single species”). Thus, one of skill in the art would also understand that there are only 22 possible species. Applicants have shown at least two of these species and their effect. Thus, Applicants have not only accounted for two species, but the two species described account for the entirety of the variation within the genus. For this reason alone, the Applicants have adequately show possession of the entire genus, satisfied the standard for written description, and respectfully request a withdrawal of this rejection.

Applicants note that regarding claim 39, the Examiner has stated that “modification of the His residue in the diphthamide domain is...non-desirable.” In support of this, the Examiner quotes the specification on page 18, lines 2-20, but in particular lines 13-14 which states that the cells with mutated EF-2 (substituted His residue) grew more slowly than wild-type. From this, the Examiner infers that the mutant is non-desirable. Respectfully, Applicants point out that the desirability of a species within the genus is not the issue nor is the rate of growth. The issue is whether Applicants have disclosed a number of species commensurate with the genus. Within this genus, clearly some species will be more desirable than others. Moreover, that the mutant

cells are slow growing ignores the fact that the cells are resistant to the diphtheria toxin which was the purpose of making the mutation. Thus, though slow growing, the His mutant cells are desirable because they are resistant to the effects of the toxin. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

REJECTION UNDER 35 U.S.C. § 103

Claims 1, 3, 5-10, 12, 13, 15-20 and 22-25 are rejected under 35 U.S.C. 103 as allegedly being obvious over Madsen et al (US 6,723,536) in view of Neville et al (WO 01/87982). Applicants respectfully traverse this rejection.

The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In *Graham*, the court set forth the following three pronged test for the determination of obvious: 1) determining the scope and content of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; and 3) resolving the level of ordinary skill in the pertinent art. Additionally, the court noted that evidence of secondary considerations would be evaluated. Here, the Examiner has stated that Applicants claim a method of expressing an immunotoxin in *Pichia pastoris* in “which methanol induction is performed at a temperature below 17.5°C.” Applicants respectfully point out that the claims have been further amended to recite methanol induction at 16.5°C and below. Accordingly, the cited art alone or in combination must teach or suggest this specific range of methanol induction temperatures to make the present claims obvious. The Examiner has conceded that “Neville et al do not teach that the temperature is below about 17.5°C.” Because Neville does not teach methanol induction temperatures below about 17.5°C it also does not provide disclosure of methanol induction temperatures at 16.5°C and below. Respectively, the cited art alone or in combination must teach or suggest this specific range of methanol induction temperatures to make the present claims obvious. Because Neville does not teach all the limitations of the claims and the Examiner must rely on the combination of Neville et al. with the teachings of Madsen et al. to teach or suggest the missing limitation methanol induction. The Examiner states that Madsen et al. teach that “[m]ethanol induction was

performed wherein the induction was performed at less than about 17.5°C (see col 7, lines 35-44)."

Contrary to the assertions of the Examiner, Applicants respectfully submit that the Madsen reference does not actually describe methanol induction below 20°C. In fact, the support provided by the Examiner does not refer to methanol induction, but rather that during harvest, methanol and pH loops are shut off. In particular, column 7, lines 38-42 state "Harvest conditions are then set, after the conditions have been achieved the fermentation process is ready for harvest. To minimize foaming, the methanol and pH loops are not shutoff until the temperature is below 20°C." [emphasis added] Further evidence to this understanding can be found on column 9, lines 37-38 where the protocol indicates that methanol flow rate is reduced and then turned off once 20°C is met. Although Madsen et al. says shutoff occurs below 20°C in column 7, to read into this statement as including temperatures at 19°C and below would run contrary to the statements on column 9 which says the flow rate is turned off once 20°C is met. Clearly Madsen et al. was recognizing a fractional temperature between when 20°C is met and when flow could be shut off, but not indicating that lower degrees were reached before methanol induction stopped. In fact, such an interpretation would run contrary to the entire reference which utilized very precise measurements (e.g., 83 hours at 26°C in column 9). If the Examiner's interpretation were true then Madsen et al. would have indicated a stopping temperature of 17, 18, or 19°C. Additionally, Applicants respectfully submit that this is certainly not the disclosure of methanol induction occurring 16.5°C and below as is now claimed.

In fact, Madsen teaches methanol induction occurs for 83 hours at 26°C (column 9, line 10 (for temperature) and line 27 (for duration)). Thus, Madsen does not disclose nor teach the limitation of methanol induction at 16.5°C and below. Accordingly, Madsen does not rescue the deficiencies in Neville. Because the cited art alone or in combination fails to teach or suggest all the limitations in the claims, the claims are not obvious. For at least this reason the claims are not obvious and the Applicants respectfully request a withdrawal of this rejection.

Moreover, Applicants respectfully submit that the methanol induction temperature of 16.5°C and below of the claims offers a significant improvement in yield - a synergistic and

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surprising result. In Figure 21D and 21E it can be seen that the yield is more than doubled when the induction temperature is changed from 23-25°C to 15°C (see page 3, paragraph [0039] for Figure legend). Applicants respectfully remind the Examiner that synergistic results and surprising results have been considered by the courts as secondary considerations which are evidence for non-obviousness. The results herein show that the increased yield from the reduced induction temperature was both synergistic (i.e., more than additive) and unexpected. Thus, the specification provides evidence of secondary considerations that weigh in favor of the Applicants which the Examiner must consider in the determination of obviousness. For at least this reason the claims are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Claims 2, 4, 11, 14, 21 and 26 are rejected under 35 U.S.C. as allegedly being obvious over Madsen et al (US 6,723,536) in view of Neville et al (WO 01/87982), and further in view of Magota et al (6,171,828) and McGrew et al (Gene, 1997, Vol 187(2), pages 193-200) and Chang et al (US 6,992,172). Applicants respectfully traverse this rejection. As noted above, Madsen alone or in combination with Neville fails to teach all the limitations of the claims. In particular, alone or in combination Madsen and Neville fail to teach methanol induction at 16.5°C and below. Accordingly, for the rejection to stand Magota, McGrew, or Chang must teach this deficiency. Importantly, none of Magota, McGrew, or Chang alone or in combination are capable of correcting the deficiency in Madsen and Neville. As none of the Examiner's cited reference, alone or in combination, teach or suggest all the limitations in the claims, the claims are not obvious. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

In view of the above amendments and remarks, reconsideration and allowance of the application are believed to be merited and are respectfully requested. The Examiner is invited to directly contact the undersigned if doing so will expedite the prosecution of this application.

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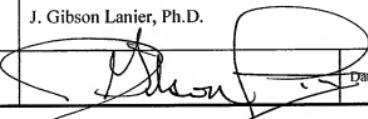
A Credit Card Payment authorizing payment in the amount of \$3050.00 which includes \$620.00 the large entity fee under 37 C.F.R. § 1.17(a)(3) for a three (3) month Extension of Time minus fees previously paid for a two (2) month extension of time, \$810.00 the large entity fee under 37 C.F.R. § 1.17(e) for a Request for Continued Examination, and \$1620 the large entity fee under 37 C.F.R. § 1.17(m) for a petition to revive an unintentionally abandoned application; a Request for Continued Examination; a Request for a three (3) month Extension of Time; and a Petition to Revive for Unintentional Abandonment are being submitted electronically. This fee is believed to be correct. However, if a fee is due, the Commissioner is hereby authorized to charge any such fee or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

BALLARD SPAHR ANDREWS & INGERSOLL, LLP


J. Gibson Lanier, Ph.D.
Registration No. 57,519

BALLARD SPAHR ANDREWS & INGERSOLL, LLP
Customer Number 36339
(678) 420-9300
(678) 420-9301 (fax)

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